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Author's reply

I write as the statistician on the paper by Mulcare and colleagues,[1] which was criticised by Kolho and Järvelä above. I wish to correct two assertions made by Kolho and Järvelä. The first is their claim that with our statistical procedure ''there is a risk of wrong conclusions being drawn'' because ''adult-type hypolactasia is difficult to assess due to inaccurate diagnostic tests''. This would indeed be true had we applied a ''naïve'' test (for example, a χ^2 test) in which we had assumed the diagnoses of hypolactasia to be without error. In fact, not only did we assume that diagnoses occurred with error, but we did not even presume to know exactly what that level of error was. Instead, our uncertainty about the true level of error was modelled in a Bayesian framework and trained using available published data on comparisons of ''true'' diagnoses (for example, based on biopsy results) and ''indirect'' diagnoses (for example, based on breath hydrogen). To accomplish this, a novel statistical method was developed, which was described by Mulcare and colleagues.[1] The fact that we incorporated these additional sources of error into our method means that the p values we obtained were not as low as they would have been had we applied a naïve test such as a χ^2 test. Our remarkable finding was that, despite this, we still found significant departures in multiple sub-Saharan African populations. This led us to reject the null hypothesis that the presence of the C/T−13910 variant alone, even with diagnostic error, could explain the published data on lactase persistence in Africa. Other reasons must be sought to explain our results, one of which is the possibility that additional genetic variants influence lactase persistence.

The second assertion by Kolho and Järvelä was that there were ''no statistics shown against the C/T−13910 variant, only speculation presented''. The meaning is unclear here. Certainly, statistics both in the sense of ''data'' and in the sense of ''inference'' were presented in our paper (see above). Our conclusions regarding the C/T−13910 variant were derived from carefully constructed statistical inference, and not mere ''speculation''.

M E Weale

Correspondence to: Dr M E Weale, University College London, Gower St, London WC1E 6BT, UK; m.weale@ucl.ac.uk

Conflict of interest: None declared.

Reference

1 **Mulcare CA**, Weale ME, Jones AL, *et al*. The T allele of a single-nucleotide polymorphism 13.9 kb upstream of the lactase gene (LCT) (C-13.9kbT) does not predict or cause the lactase-persistence phenotype in Africans. *Am J Hum Genet* 2004;**74**:1102–10.

''Cannabis hyperemesis'' causation questioned

The authors describe a number of cases of a bizarre syndrome of severe vomiting, abdominal symptoms leading to dehydration, in combination with repetitive bathing behaviour (*Gut* 2004;**53**:1566–70). They have concluded that these symptoms are due to cannabis use.

Cannabis has been consumed for many centuries and is currently used by millions of people in many countries. It is hard to believe that a distinctive syndrome caused by cannabis has never been noted before by users or clinicians.

The authors assert that cannabis laws are particularly liberal in South Australia. Four Australian jurisdictions now have a cannabis expiation notice system which South Australia first introduced in 1986. The other four Australian jurisdictions have variations on a bond system. Several European countries have far more lenient legislative arrangements. After over a generation of liberalisation of cannabis laws in many countries around the world, there is little evidence of a subsequent increase in cannabis use.

In a comparative study using the same methodology, the prevalence of cannabis use in more ''liberal'' Amsterdam was lower than in the more ''punitive'' San Francisco.[1]

The title of the paper, ''Cannabinoid hyperemesis'' is unduly presumptive. Some of these cases appeared to improve with abstinence and then relapsed when patients were ''rechallenged'' with cannabis, but neither the patients nor the authors appear to have been blinded in the rechallenge. The proposed biological explanation is weak.

We suggest that alternative explanations need to be sought for these cases. This syndrome should not be accepted as being caused by cannabis without additional reports and other evidence.

A Byrne, R Hallinan
Byrne Surgery, Sydney, Australia

A Wodak
St Vincent's Hospital, Darlinghurst, New South Wales, Australia

Correspondence to: Dr A Byrne, Byrne Surgery, 75 Redfern St, Redfern, 2016, Sydney, Australia; ajbyrne@ozemail.com.au

Dr Wodak is President of the Australian Drug Law Reform Foundation which supports the taxation and regulation of cannabis.

Reference

1 **Reinarman C**, Cohen PDA, Kaal HL. The limited relevance of drug policy: Cannabis in Amsterdam and in San Francisco. *Am J Public Health* 2004;**94**:836–42.

Authors' reply

We would like to thank Byrne *et al* for their interest in our paper (*Gut* 2004;**53**:1566–70). It should be noted that we undertook an observational study by necessity. Cannabis is an illegal drug and double blind control trials with illicit substances are prohibited and unethical. The assertion that cannabis has been ''consumed for many centuries'' needs to be tempered with the fact that cannabis has been grossly under-researched clinically and, as we have shown with this syndrome, nowhere near fully understood in its neuropharmacology or paradoxical actions. Since publication of our article, other authors have published similar findings to ours and drawn the same conclusions.[1]

J H Allen
Department of Medicine, Mt Barker Hospital, Mt Barker, South Australia, Australia

G M de Moore
Department of Psychiatry, Westmead Hospital, Westmead, New South Wales, Australia

R Heddle
Department of Gastroenterology, Repatriation General Hospital, Daw Park, South Australia, Australia

J C Twartz
Department of Medicine, Ashford Hospital, Ashford, South Australia, Australia

Correspondence to: Dr J H Allen, Department of Medicine, Mt Barker Hospital, Wellington Rd, Mt Barker, South Australia 5255, Australia; gjballen@bigpond.com

Conflict of interest: None declared.

Reference

1 **Roche E**, Foster PN. Cannabinoid hyperemesis: not just a problem in Adelaide Hills. *Gut* 2005;**54**:731.

IL-1 gene cluster and *TNFA*−307 polymorphisms in the risk of perforated duodenal ulcer

Helicobacter pylori virulence markers have been associated with duodenal ulcer (DU) but there are few studies evaluating host factors such as cytokine polymorphisms and, to the best of our knowledge, no study has evaluated these polymorphisms as risk factors for perforated DU. We investigated associations among interleukin 1 (IL-1) cluster and tumour necrosis factor α (*TNFA*)−307 polymorphisms, and DU and perforated DU in a non-Caucasian population. We included 223 patients with DU, 29 patients with perforated DU, and 541 blood donors. *H pylori* status was investigated by culture, preformed urease test, stained smear, polymerase chain reaction (PCR), and the ^{13}C-urea breath test. *cag*A status was assessed by PCR. In the blood donors, *H pylori* status and *cag*A status were determined by serology. *IL-1B*−511/−31, *IL-1RN*, and *TNFA*−307 polymorphisms were genotyped by PCR, PCR/restriction fragment length polymorphism, or PCR/confronting two pair primers.[1] Data were analysed in logistic models. The loci did not deviate significantly from the expected Hardy-Weinberg distribution in the control group. *IL-1B*−511T and *IL-1B*−31C polymorphic alleles were in almost complete linkage disequilibrium in all three groups ($p<10^{-6}$). We thus restricted further analyses to *IL-1B*−31. No polymorphism remained associated with non-complicated DU after correcting for age and sex, but the *IL-1RN*2 carrier showed a trend towards increasing DU risk ($p = 0.06$; odds ratio (OR) 1.43 (95% confidence interval (CI) 0.99–2.05)). Regarding perforated DU, in the multivariate analysis, *IL-1B*−31C and *TNFA*−307A alleles remained inversely associated with the disease, even after inclusion of confounding factors (table 1). *cag*A status remained the strongest factor associated with either uncomplicated ($p = 0.00$; OR 4.29 (95% CI 2.63–6.98)) or perforated DU. The other polymorphisms were not associated with perforated DU (table 1).

Although morbidity from peptic DU has greatly decreased since early studies on *H pylori* infection,[2] little change was observed